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TCNU (LS 2667), a New Active Drug in the Treatment of Advanced Colorectal Cancer

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Abstract—*Fifty-seven patients with advanced measurable or evaluable colorectal cancer not previously treated with chemotherapy and tumor manifestations from colorectal cancer were treated with tauromustine (TCNU), a new nitrosourea with a therapeutic index against murine tumors better to or equal to that of the established nitrosoureas. The dose was* 130 mg/m^2 *orally q* 5 *weeks. There were one CR and seven PR, for an overall response rate of* 14%. *Responding sites included the liver (one CR and two PR), lung (four PR) and lymph nodes (two PR). The median duration of response was* 33+ *weeks* (21+ *to* 34 *weeks). The main dose limiting toxicity was myelosuppression which seemed to be cumulative. Subjectively, the drug was well tolerated although most patients experienced nausea and vomiting for some hours.*

It is concluded that TCNU is a well tolerated compound with limited, but definite antitumor activity against colorectal cancer and that further studies in this disease could be of interest.

INTRODUCTION

SINGLE AGENT therapy has been extensively studied in colorectal cancer [1]. Response rates have rarely exceeded 20–25% with no major impact on survival. Regarding these consistent low response rates, there is an urgent need for clinical screening of new drugs in colorectal carcinoma.

Tauromustine (TCNU, LS 2667) is a new nitrosourea based on taurine, with the amino group nitrogen constituting one of the nitrogens of the nitrosourea. The sulfonic acid group of taurine has furthermore been transformed into a dimethylamino sulfonyl group. The aim of these molecular modifications was to develop a nitrosourea with an improved therapeutic index. The changes made the compound more hydrophilic and resulted in higher experimental cytotoxicity. In experimental tumors TCNU has shown equal or better activity than other nitrosoureas [2]. In phase I trials activity has been found in non-small cell lung cancer, melanoma and breast cancer [2–4].

In phase I studies TCNU was given orally. At dose levels of 70 mg/m^2 consistent hematologic toxicity was observed. This included thrombocytopenia, anemia and leucopenia. Thrombocytopenia was dose limiting. The nadir of the thrombocytes was usually observed at 3 weeks with recovery within 4–5 weeks after drug administration, while the nadir of leucocytes usually occurred 2 weeks after the nadir of thrombocytes. Nausea and vomiting were seen in virtually all patients at dose levels of $\geq$90 mg/m^2. Based on toxicity as related to prior treatment, the recommended dose in phase II studies for previously untreated patients was 130 mg/m^2 orally every 5 weeks.

The aim of the present phase II study was to determine if TCNU could achieve complete or partial responses in advanced colorectal cancer and to further characterize its toxic effects.

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MATERIAL AND METHODS

Patients with histologically confirmed, surgically incurable and progressive colorectal adenocarcinoma were entered. Eligibility criteria further included measurable or evaluable previously non-irradiated lesions, no previous chemotherapy, no brain involvement or leptomeningeal disease, performance status (WHO) <3, life expectancy $\geq$3 months, age $\leq$75 years, white blood cell counts (WBC) $\geq 4.0 \times 10^9$/l, platelet counts $\geq 100 \times 10^9$/l, serum bilirubin level $\leq$35 μmol/l and serum creatinine $\leq$120 μmol/l. Initial work-up consisted of history, physical examination, complete blood cell counts, routine chemistry profile and chest X-ray. Complete blood cell counts were repeated weekly during treatment.

TCNU was given at a starting dose of 130 mg/m^2 every 5 weeks and was supplied in tablets of 25 and 50 mg, stored at 4°C.

Dose adjustments were planned for each course according to WBC and platelet nadirs in the previous course. The dose was increased by 20% if nadir WBC was superior to 4.0 and nadir platelets superior to 100 × 10^9/l. The dose was reduced by 25% if nadir WBC was between 1.0 and 2.0, or nadir platelets between 25 and 50 × 10^9/l, and reduced by 50% if these values were inferior to 1.0 and 25 × 10^9/l respectively. Subsequent doses of TCNU were delayed by 1 week if toxicity persisted at the day of scheduled retreatment.

If WBC and platelet counts were <4.0 or 100 × 10^9/l 7 weeks after the last dose the patient went off study. Treatment was discontinued if there was disease progression after two courses or in cases of a rapid progression at the time the second course was planned. In cases of remission, TCNU was continued until progressive disease or severe toxicity developed.

All patients were evaluated according to the WHO criteria, defined as follows: complete response—disappearance of all known disease, determined by two observations not less than 5 weeks apart; partial response—decrease by at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions determined by the observations not less than 5 weeks apart; progressive disease—a 25% or more increase in the size of at least one indicated lesion or the appearance of a new lesion. When the progression was observed before a second course of TCNU was given, the patient was considered as an early progression.

The duration of partial response was measured from the date of first treatment administration to the date of the disease.

RESULTS

A total of 66 patients were treated. Five of these cases were ineligible, because of prior chemotherapy (one case), and lack of histological proof of malignancy (four cases).

The characteristics of the 61 eligible patients are given in Table 1. Mean age was 59 years, median performance status 1 (0 in 30 cases, 1 in 26 patients and 2 in six patients). Nine patients had received prior radiotherapy, but target lesions were not in the irradiated field.

Table 1. Patient characteristics

Number of eligible patients	61
Median age in years (range)	59 (39–73)
Median WHO performance score (range)	1 (0–2)
Prior radiotherapy	9
Number of indicator lesions	
Lung	43
Liver	17
Lymph nodes	8
Skin	5
Soft tissue	4
Median number of courses (range)	2 (1–6)

Among the 61 eligible patients, four were not evaluable for response: three died within 4 weeks after the start of TCNU (early non-toxic death) and one patient refused treatment.

Out of the 57 evaluable patients, one CR and seven PR were observed (Table 2). The overall response rate was estimated at 14%, with a 95% confidence interval (CI) ranging from 5 to 23%. If all eligible patients were considered, the response rate became 13%, and the 95% CI 4–21%. The median duration of response was 33 weeks (actuarial estimate) with a range of 22+ to 34 weeks. Responding sites included the liver (one CR + three PR), lung (five PR), lymph nodes (one PR) and soft tissues (one PR). The main toxicity of TCNU consisted of myelosuppression (Table 3). For the first course of treatment, median WBC and platelet nadirs (× 10^9/l) were 4.5 (0.7–11.7) and 83 (12–600), respectively. For all cycles the corresponding values were 2.8 (0.7–11.0) and 69

Table 2. Effect of TCNU in colorectal cancer

Number of evaluable patients	Response (No. of patients) CR	PR	NC	PD	(EPD*)
57	1	7	7	42	(7)

*Early progressive disease.

Table 3. Hematologic toxicity

	Nadir WBC × 10^9/l First/all courses	Nadir platelets × 10^9/l First/all courses
Median	4.5/2.8	83–69
Range	0.7–11.7/0.7–11.0	12–600/11–372
Day nadir, median (range)	35 (10–40)	27 (6–30)
Day recovery, median (range)	42 (15–51+)	34 (25–50+)

Table 4. Non-hematological toxicities

	WHO grade 1–2
Nausea/vomiting	50 (1)*
Diarrhea	7 (1)*
Alopecia	3
Oral	2
Hemorrhage (oral petecchiae)	1
Infection	2
Neuropathy	3
Sedation	2

*WHO grade 3.

(11–372), suggesting cumulative myelosuppression. Other side effects (Table 4) consisted of vomiting observed in 81% of the patients, and diarrhea occurring in 13% of the patients. Alopecia and mucositis were minimal.

DISCUSSION

In an analysis of phase II trials from 1970 to 1985 colon cancer was the least responsive tumor studied. Among 42 drugs (not including 5-fluorouracil) tested in this disease in >200 separate studies involving >2500 evaluable patients, there were no active drugs apart from the 5-fluorouracil analog tegafur [5].

In the present study the response rate to TCNU among 57 patients was 14% including one CR of multiple liver metastases documented on CT scan and normalization of CEA. This patient subsequently progressed in the liver and autopsy verified the diagnosis. Our finding is of interest also because other nitrosoureas such as BCNU, CCNU and MeCCNU only occasionally have been reported to induce tumor regression [6]. Moreover, although nausea and vomiting regularly occurs, these side-effects usually last only for hours and the drug is in general well tolerated by most patients.

In conclusion, TCNU is a well tolerated compound with limited, but definite, antitumor effect against colorectal cancer. Since the most common used drug in advanced colorectal cancer today is 5-fluouracil, a randomized study between TCNU and 5-fluorouracil is being planned by groups outside the Early Clinical Trials Group.

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